Remarks

The above amendment and the following remarks are in reply to the Office Action mailed July 30, 2002. Applicants will respond to the issues raised in the Office Action in the order presented by the Examiner.

Claim Rejections-35 U.S.C. §102

Claims 11-12 stand rejected under §102(b) as anticipated by Lubinski et al (Journal of Virology 72(10): 8257-8263, 1998). Lubinski et al., show a gC-deficient HSV in a sterile physiologically balanced solution at a titer of 5×10^4 pfu. The Examiner will note that Applicants have amended claims 11-12 to recite that the pharmaceutical composition also contains a "carrier." The term "carrier" is defined in Applicants' specification on page 13, lines 19-25, and is included in the cited U.S. patent no. 5, 962, 429. Applicants respectfully submit that this amendment obviates the rejection, and thus request that it be withdrawn.

Claim Rejections-35 U.S.C. §103

Claims 1-4 and 7-13 stand rejected under 103(a) as being unpatentable over Rabkin et al., (U.S. patent no. 6, 379, 674) in view of Lubinski et al., (Journal of Virology 72(10): 8257-8263, 1998). Rabkin et al., teach a method for treating a neoplasm comprising administering a mutant herpes simplex virus to the neoplasm, and a chemotherapeutic may also be used with the virus. As the Examiner has stated, Rabkin et al., do not specify that a skilled practitioner of this art would elect to use a gC mutant virus. The Examiner further states that Lubinski et al., teach that HSV gC mediates immune evasion and inhibits complement mediated lysis of infected cells, AND since the purpose of Rabkin is to induce an immune response against the infected tumor cells, one of ordinary skill in the art would have been motivated to use a gC-defective HSV, for the purpose of improving the immune response induced by the infected cells and improving the lysis of infected tumor cells. Applicants respectfully disagree with the Examiner, and request that the rejection be withdrawn for the following reasons.

First, gC of HSV-1 consist of several functionally distinct domains. One of them, consisting of amino acids 33-123 is responsible for binding to heparan sulfate, while others are thought to play a role in the virulence activity of the virus. See, Lubinski et al., (J. of Exp. Med. 11: 1637-1646, 6 December 1999) also cited by the Examiner. There it

is stated that removing the heparan binding domain of gC, or amino acids 33-123, does NOT affects its virulence activity when compared to wild-type virus, as tested in a C3 (complement 3) knock out mouse. Recall that Applicants' exemplary herpes virus also lacks amino acids 33-123. The Examiner is referred to page1644, first full paragraph and particularly lines 10-15, where it is stated regarding gC: "This mutant virus lacks gC amino acids 33-123, identified as an important domain for gC-mediated attachment to heparan sulfate in vitro (40). Yet this virus shows no difference in virulence from wild-type virus in C3 knockout mice..." (emphasis added).

Thus, Applicants respectfully submit that it would not have been obvious to a skilled practitioner of this art at the time that Applicants made their invention, that one could use a HSV-1 virus that has reduced heparan binding activity to kill tumor cells. Clearly, this aspect of Applicants' invention, the realization that the invention gC viruses' properties could be used to kill cancer cells, and moreover, while sparing normal cells, is absent from the cited references. Indeed, based on the Lubinski et al's J. Exp. Med. paper, one would expect that the invention viruses would show no such selectively. This unexpected result, shown and claimed by the Applicants, coupled with no showing or suggestion in either the primary or secondary reference, render their invention unobvious.

Second, there are many gC-defective viruses in the scientific literature, and the properties of these viruses relating to attachment to a host cell, killing of the host cell, if it occurs at all, and by what mechanism is unclear. For example, regarding cell attachment, on page 8258, under "Results," first paragraph, 2nd sentence, Lubinski et al., state that "Some strains of gC-null virus are defective in virus attachment to cells (49), whereas others are normal (20)..." Further on page 8261, under "Discussion," first paragraph , lines 6-11, it is stated that "Studies have reported that HSV-1 gC also mediates virus attachment to cell surface heparan sulfate (23, 49) and is required for apical infection of polarized cells (42). However, other reports using different HSV-1 gC-null strains and different cell lines noted that gC is not required for virus attachment or infection of polarized epithelial cells (20)."

Clearly, this confusion in the scientific literature regarding the properties of gC adds further support to Applicants' position that their discover to use the instant viruses for treating cancer is unobvious. Indeed, at the time that Applicants made their invention

it cannot be said that there was the slightest motivation in the literature to use the instant viruses as claimed.

Considering the above arguments, Applicants have amended the claims to recite that the instant methods involve a herpes virus that does not produce "a functionally active wild-type glycoprotein C polypeptide capable of binding heparan sulfate."

Claims 5-6 stand rejected under 103(a) as being unpatentable over Rabkin et al (U.S. patent no. 6, 379, 674) in view of Lubinski et al (Journal of Virology 72(10): 8257-8263, 1998) as applied t claims 1-4 and 7-13 above, and further in view of Sunstrum et al., (Virus Research 11: 17-32, 1988).

Based on Applicants' views of Rabkin et al., and Lubinski et al., presented above, and the claims as now amended to recite that Applicants' methods claims involve a virus that does not produce "a functionally active wild-type glycoprotein C polypeptide capable of binding heparan sulfate," it is respectfully submitted that these references do not show or suggest Applicants' invention, nor do they provide the motivation to make the invention.

Regarding the Sunstrum et al., reference it is not seen how it provides the motivation to make the instant invention for several reasons. There is no showing or suggestion in the reference that the gC⁻39 virus could be used to treat cancer. Second, even the basic biological activities of the gC⁻ 39 virus are in conflict in the scientific literature, including the Sunstrum et al., reference. The Sunstrum et al., reference, which was published in 1988, states in the Summary, last sentence on page 17, based on work with gC⁻ 39 virus that "gC is not a virulence determinant ...." Importantly, in the second Lubinski et al., publication (J. of Exp. Med. 11: 1637-1646, 6 December 1999), it is stated that "this mutant virus lacks gC amino acids 33-123, identified as an important domain for gC-mediated attachment to heparan sulfate in vitro (40). Yet this virus shows NO difference in virulence from wild-type virus in C3 knockout mice...." Considering that Lubinski et al., is a 1999 publication, Applicants submit that if anything the cited references when considered in combination teach away from using a gC⁻ 39 virus to treat cancer. Indeed, based on the combination of references, a skilled practitioner of this art would not choose a gC⁻39 virus to kill tumor cells with the hope of sparing normal cells

since one would expect no difference in its virulence activity from the wild type herpes virus.

Applicants have considered the remaining references cited by the Examiner, and find that they are no more relevant to a determination of the patentability of Applicants' invention than those discussed above.

The Examiner will note that Applicants have made amendments to claims 7 and 10. Claim 7 now recites "normal" as the type of cell intended. Claim 10 has deleted "cancer" and substituted therefore is "neoplasm." The amendment is made to provide proper antecedent basis for "neoplasm" which is recited in Claim 1.

In view of the above Amendments and Remarks, reconsideration of the pending claims is requested. The Examiner is encouraged to telephone the undersigned if a call to Applicants' attorney will expedite prosecution of their patent application.

The Commissioner is hereby authorized to charge any fees associated with this communication to Deposit Account No. 15-0615, for any matter in connection with this response, including any fee for extension of time, which may be required.

Respectfully submitted,

Date: 1/30/03

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Appendix A
Amendments showing modifications

In the claims:

1. A method for treating a neoplasm comprising cells, comprising:

administering to said neoplasm an amount of a mutant human herpes simplex virus which is oncolytic to cells in said neoplasm, wherein said virus does not produce a functionally active wild-type glycoprotein C polypeptide capable of binding heparan sulfate.

2. A method of claim 1, wherein said virus comprises a deletion in the UL44 gene which codes for heparan binding of glycoprotein C polypeptide.

4. A method of claim [2] 1, wherein said virus comprises an insertion in the UL44 gene which codes for heparan binding of glycoprotein C polypeptide.

7. A method of claim 1, wherein said virus is impaired in its ability to infect, or attach to the surface of normal cells as compared to the wild-type parental strain.

9. A method of claim 1, wherein said [cancer] neoplasm is an adenocarcinoma.

10. A kit comprising a mutant human herpes simplex virus which is oncolytic to cells in a neoplasm, wherein said virus does not produce a functionally active wild-type glycoprotein C polypeptide capable of binding heparan sulfate and a chemotheraputic agent.

11. A pharmaceutical composition comprising a mutant human herpes simplex virus wherein said virus does not produce a functionally active wild-type glycoprotein C polypeptide coded for by the UL 44 gene, and a carrier in a sterile physiologically balanced solution.